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(54) Spray dried acetaminophen.

(57) A therapeutic taste-neutral powder form of acetaminophen is obtained by spray-drying a suspension of acetaminophen in a solution of a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters. The powder can be formulated into fast dissolving dosage forms, chewable tablets and the like.

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SPRAY DRIED ACETAMINOPHEN

This invention relates to a novel therapeutic form of spray dried acetaminophen having a neutral taste which can be formulated into for example, fast dissolving dosage forms as described in United States Letters Patent Nos. 4,305,502 and 4,371,516 and UK Patent Specification 1,548,022. More specifically this invention relates to a spray dried powder formed by spray drying a suspension of acetaminophen in a solution of a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean molecular weight of 150,000. The spray dried powder may be taste-neutral. By "taste-neutral" it is meant that the powder has essentially no taste and is not sweet nor bitter.

Acetaminophen (otherwise known as paracetamol), a widely used analgesic and antipyretic, is not palatable enough to be used in chew-type tablets for those people who do not swallow whole solid-type dosage forms.

The use of flavour agents e.g. chocolate, banana, orange, lemon, licorice, root beer and raspberry, in particular, have been proposed for bitter tasting drugs. These agents are not dependable masking ingredients. Mint flavours can be useful in ameliorating a chalky taste parameter. Bitter properties, however, are very difficult to mask to any great extent, particularly, when they do not mimic the expected natural taste of the flavour agent.

The fast dissolving dosage forms described in United States Letters Patent Nos. 4,305,502 and 4,371,516 and UK specification 1,548,022 are manufactured to disintegrate in water within ten seconds e.g. within five seconds or less and hence dissolve rapidly in the saliva of the mouth.

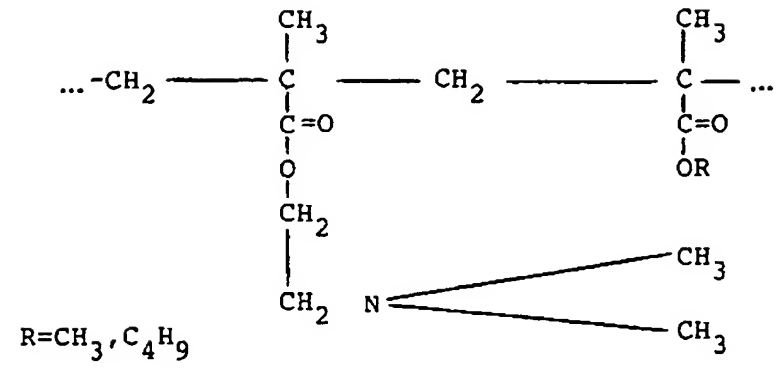
Such dosage forms for oral administration can comprise a network of a pharmaceutically acceptable water-soluble or water dispersible carrier material (e.g. gelatin) carrying a unit dosage of pharmaceutical substance, the carrier being inert towards the pharmaceutical substance, the network having been obtained by subliming solvent from a composition in the solid state, the composition comprising the pharmaceutical substance and a solution of the carrier material in a solvent such that the dosage form is capable of being disintegrated by water within ten seconds. Heretofore the use of such dosage forms was restricted to pharmaceuticals which had a neutral taste or a slightly disagreeable taste which could be masked by a flavoring agent. Pharmaceuticals with a bitter taste such as acetaminophen however, could not heretofore be used in such dosage forms.

According to this invention, a novel therapeutic taste-neutral powder form of spray-dried acetaminophen is provided which can be formulated into fast dissolving dosage forms, chewable tablets and the like. The powder is formed by spray drying a solution having dissolved therein a copolymer, cationic in character, having a mean molecular weight of 150,000, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters, the solution having finely divided acetaminophen suspended therein.

The invention particularly provides a therapeutic powder form of spray-dried acetaminophen which consists essentially of acetaminophen and a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean molecular weight of about 150,000, the powder having been spray-dried from a suspension of the acetaminophen in a solution of the copolymer in an organic solvent selective for the copolymer.

According to another aspect of this invention, a pharmaceutical dosage form for oral administration as a solid is provided, which dosage form can be disintegrated by water at 37°C within ten seconds, and comprises as the pharmaceutical agent incorporated therein the taste neutral powder form of spray-dried acetaminophen of this invention.

The acetaminophen useful in this invention may be the pharmaceutical grade. An example of the copolymer is that available as Eudragit E 100 from Rohm Pharma GmbH, Darmstadt, West Germany as light yellow granules containing at least 98% of dry lacquer substance having an acid value of 180 mg KOH/g. The structural formula is based upon:



The copolymer is commercially available from Rohm Tech, Inc, 195 Canal Street, Malden, MA 02148, USA, United States representative of Rohm Pharma GmbH, West Germany.

The weight percent of acetaminophen in the taste neutral powder can be from about 60 to 74% by weight and the weight percent of the copolymer can range from 26% to 40% by weight. At 26% by weight of copolymer, there is a slightly bitter taste but at about 30% (e.g. as exemplified in Examples 1 and 2 below) and above the powder is taste neutral.

The solvent for the copolymer can be, for example, methylene chloride, acetone or an alkanol but must be an organic solvent selective for the copolymer and in which the acetaminophen is not soluble to any great extent.

Spray dryers can be of the usual laboratory or commercial type. Suitable spray dryers are manufactured by Buchi Laboratoriums-Technik AG, by the Anhydro Company of Attleboro, Massachusetts and by Niro Atomizer Inc., of Colombia, Maryland.

The spray dryer employed in the following examples was a Niro Portable Spray Dryer, Model No. 21231-0001. The operating conditions include a variable air inlet temperature, a variable outlet temperature, a variable air pressure of compressed air driving the atomizer wheel, and a variable feed rate.

The following examples illustrate the invention:

EXAMPLE I

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Ingredient in Suspension	Weight % Solids in Suspension	Weight % Solids in powder	Grams Ingredient in suspension
Acetaminophen	4.50	4.50	70.09	270
Methylene Chloride	73.58	———	———	4414.8
Eudragit E-100	1.92	1.92	29.91	115.2
Methylene Chloride	20.00	———	———	1200
Total:	100.00	6.42	100	6000 g.

The acetaminophen was suspended in the 4414.8 grams of methylene chloride contained in a stainless steel mixing vessel with the aid of a Lightnin mixer. The Eudragit E-100 was dissolved in the remaining methylene chloride in a separate stainless steel mixing vessel and the contents of the two mixing vessels were then admixed and transferred to the feed hopper of the Niro Portable Spray Dryer.

The spray drier was operated with a feed rate of 60 grams per minute and initially at ambient inlet air temperatures. The air pressure was 4.8 bar. After a first chamber sweep, the chamber powder was observed to be slowly adhering to the walls and had a definite solvent odor. The air inlet heater was turned on so as to produce an outlet temperature of 25° - 30°C. The powder from a second chamber sweep had less solvent odor and no powder adherence was noted. The yield of spray dried powder was 91.12 %, 140 grams from the cyclone and 21.1 grams from the chamber. The product from the cyclone was a white, fine powder and the product from the chamber was a fine white powder but not free-flowing.

The product from the cyclone, when tasted, produced no bitterness characteristic of acetaminophen but a slight solvent odor and taste. The product from the chamber produced a very slight bitterness with only a slight solvent odor and taste.

EXAMPLE 2

In this example, the solids content of the suspension was increased as follows:

Ingredient	Weight % Ingredient in Suspension	Weight % Solids in Suspension	Weight % solids in powder	Grams Ingredient in suspension
Acetaminophen	13.50	13.50	70.09	270.0
Methylene chloride	30.74	———	———	614.8
Eudragit E-100	5.76	5.76	29.91	115.2
Methylene Chloride	50.00	———	———	1000.0
Total:	100.00	19.26	100.00	2000.0g.

The spray dryer was operated with a feed rate of 80 grams per minute with an air pressure of 4.6 bar declining to 3.8 bar. The air inlet heater was turned on so as to produce an outlet temperature of 25° to 30°C with an air pressure of 4.6 bar declining to 3.8 bar. The yield of spray dried product was 304.1 grams, 158.6 grams from the cyclone and 145.5 grams from the chamber, which is 78.95 % of the theoretical yield.

The product from each of the cyclone and the chamber, when tasted produced no bitterness in the mouth. There was a very slight taste and odor of solvent.

Dissolution data were obtained on capsules containing the spray product of this example using the USP procedure and using gastric juice. The spray dried product in the amount of 114.5 milligrams containing 80 milligrams of acetaminophen was placed in each capsule and six capsules were used in each test. In the USP procedure at a pH of 5 to 7, the data show that at least 94 % of the control dissolved in 10 minutes while no more than 10 % of the spray dried product dissolved in 10 minutes. In the procedure using gastric juice instead of water, 80 % of the spray dried product dissolved in less than 10 minutes.

EXAMPLE 3

In this example, the feed mixture to the spray dryer was composed of the following materials;

Ingredient	Weight % Ingredient in Suspension	Weight % Solids in Suspension	Weight % Solids in powder	Grams Ingredient in 500 grams suspension
Acetaminophen	4.50	4.50	73.77	22.50
Methylene chloride	77.90	____	____	389.50
Eudragit E-100	1.60	1.60	26.23	8.00
Methylene Chloride	16.00	____	____	80.00
Total:	100.00	6.10	100	500.00 grams

The acetaminophen was suspended in the first portion of methylene chloride contained in a stainless steel mixing vessel with the aid of a Lightnin mixer. The Eudragit E-100 was dissolved in the remaining methylene chloride in a separate stainless steel mixing vessel and the contents of the two mixing vessels were then admixed and transferred to the feed hopper of the Niro Portable Spray Dryer.

The spray drier was operated with a feed rate of 65 grams per minute and initially at ambient inlet air temperatures. The air pressure was 4.6 bar.

The yield of spray dried powder was 78. 13%, 6.16 grams from the cyclone and 17.67 grams from the chamber. The product was a fine white, free-flowing powder.

The product, when tasted, produced a very slightly bitter taste characteristic of acetaminophen and a slight solvent odor and taste.

EXAMPLE 4

This example describes the preparation of fast dissolving dosage forms using the spray dried taste-neutral acetaminophen of Example 1 and other ingredients as follows:

Ingredients	Weight % suspension	Grams in suspension
Gelatin, BY 19/50	4.0	10.00
Mannitol, granular	3.0	7.50
Deionized water	67.10	167.75
NUTRASWEET, NF	1.20	3.00
Cherry # 271	0.40	1.00
Cream Flavor #59.200/A	0.20	0.50
Sodium lauryl sulfate	0.10	0.25
Croscarmellose sodium, Type A	1.00	2.50
Powder, Example 1	23.0	57.50

The procedure for preparing a batch of the above suspension takes place in two stages, i.e. the preparation of the gelatin base and the addition of the pharmaceutical agent.

The gelatin base is prepared by adding the gelatin to the deionized water at 30°C and mixing until the gelatin is dissolved. The solution is then cooled to 25°C and the mannitol, the sodium lauryl sulfate, the sweetener, and the flavors are separately added and dissolved.

The croscarmellose sodium in powder form (AcDiSol) and the taste-neutral spray dried acetaminophen powder are dry mixed and screened through a 20 mesh screen. The mixed powder is added to the gelatin solution and further admixed with a homomixer for thirty minutes to form a uniform dispersion.

The freeze drier employed in this example was a Virtis 25 SRC Model Freeze Drier. The fast dissolving dosage forms were prepared by dosing 500 milligrams of the suspension of acetaminophen into each well in a thermoformed blister tray containing 10 wells per tray. The filled trays were placed in a larger tray containing a dry ice-methanol mixture. When the suspension in the wells were frozen, the samples were placed on the freeze dryer trays at a shelf temperature of -45°C.

When the samples had reached a temperature of -45°C, as determined by a probe in a well, the condenser was turned on and the freezer turned off. The condenser temperature was brought to between -40° and -45°C and the vacuum was turned on to between 50 and 60 millitorrs. The heater was then turned on and the shelf temperature was adjusted to 50°-55°C. The heat-dry cycle lasted for 4 hours. The vacuum, the condenser and the heater were turned off and the samples removed. The wafers from each batch were removed from the wells in the trays. They were white in color and each weighed about 165 milligrams of which about 80 milligrams were acetaminophen. The wafers from each batch when placed on the tongue exhibited a cherry/cream flavor with a very slight bitter aftertaste. When placed in water at 37°C the wafers disintegrated in less than ten seconds.

EXAMPLE 5

This example describes the preparation of fast dissolving dosage forms using the spray dried taste neutral acetaminophen of Example 2 and other ingredients as follows:

Ingredients	Weight % suspension	Grams in suspension
Gelatin, By 19/50	4.0	10.00
Mannitol, granular	3.0	7.50
Deionized water	67.10	167.75
NUTRASWEET, NF	1.20	3.00
Cherry #271 Cream Flavor #59.200/A	0.40	1.00
	0.20	0.50
Sodium lauryl sulfate	0.10	0.25
Croscarmellose sodium, Type A	1.00	2.50
Powder, Example 2	23.0	57.50

The procedure for preparing the suspension and the procedure for freeze drying the suspension were essentially the same as in Example 4. The wafers when placed on the tongue exhibited a cherry-cream flavor with a very slight bitter aftertaste. When placed in water at 37°C the wafers disintegrated in less than ten seconds.

Claims

1. A therapeutic powder form of spray-dried acetaminophen which consists essentially of acetaminophen and a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean molecular weight of about 150,000, the powder having been spray-dried from a suspension of the acetaminophen in a solution of the copolymer in an organic solvent selective for the copolymer.

2. A powder as claimed in Claim 1 which consists essentially of, based upon the weight of the powder, 60 to 74% by weight of acetaminophen and 26% to 40% by weight of the copolymer.

3. A powder as claimed in Claim 2 which comprises about 30 to 34% by weight of the copolymer.

4. A powder as claimed in any one of the preceding claims in which the solvent for the copolymer is methylene chloride, acetone or an alkanol.

5. A process for preparing a therapeutic powder form of spray-dried acetaminophen consisting essentially of acetaminophen and a copolymer, cationic in character, based upon dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean molecular weight of about 150,000 which comprises spray-drying a suspension of the acetaminophen in a solution of the copolymer.

6. A pharmaceutical dosage form for oral administration as a solid, which dosage form can be disintegrated by water within ten seconds characterised in that it contains a therapeutic powder as claimed in any one of Claims 1 to 4.

7. A solid pharmaceutical dosage form for oral administration which comprises a network of pharmaceutically acceptable water-soluble or water-dispersible carrier material carrying a unit dosage of pharmaceutical substance, the carrier material being inert towards the pharmaceutical substance , the network having been obtained by subliming solvent from a composition in the solid state, the composition comprising the pharmaceutical substance and a solution of the carrier material in a solvent, such that the solid dosage form is capable of being disintegrated by water within ten seconds characterised in that the pharmaceutical substance is a therapeutic powder as claimed in any one of Claims 1 to 4.

8. A chewable tablet comprising a powder as claimed in any one of Claims 1 to 4.

Claims for the following Contracting States: ES, GR

1. A process for preparing a therapeutic powder form of spray-dried acetaminophen consisting essentially of acetaminophen and a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean molecular weight of about 150,000 which comprises spray-drying a suspension of the acetaminophen in a solution of the copolymer in an organic solvent selective for the copolymer.

2. A process as claimed in Claim 1 in which the powder consists essentially of, based upon the weight of the powder, 60 to 74% by weight of acetaminophen and 26% to 40% by weight of the copolymer.

3. A process as claimed in Claim 2 in which the powder comprises about 30 to 34% by weight of the copolymer.

4. A process as claimed in any one of the preceding claims in which the solvent for the copolymer is methylene chloride, acetone of an alkanol.

5. A process as claimed in any one of claims 1 to 4 in which the resulting therapeutic powder is incorporated as the pharmaceutical substance in a pharmaceutical dosage form for oral administration as a solid, which dosage form can be disintegrated by water within ten seconds.

6. A process as claimed in any one of claims 1 to 4 in which the resulting therapeutic powder is incorporated as the pharmaceutical substance in a chewable tablet for oral administration.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 30 9255

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y,D	FR-A-2 366 835 (JOHN WYETH & BROTH. LTD) * Claims 1-4; page 2, lines 32-38 *	1,4-8	A 61 K 47/00 A 61 K 9/20 A 61 K 31/165
Y	EP-A-0 040 472 (MALLINCKRODT INC.) * Claims 1-3 *	1,4-8	
Y	FR-A-2 139 825 (MEIJI SEIKA KAISHA LTD) * Claims 1-14 *	1,4-8	
Y,P	EP-A-0 212 641 (G.D. SEARLE & CO.) * Page 4, lines 12-16; page 5, lines 6-29; page 7, line 27 - page 8, line 2; page 8, lines 8-21 *	1,4-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K 47/00 A 61 K 9/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04-02-1988	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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